PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 207/34, A61K 31/40 — A1

(11) International Publication Number: WO 99/00364

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/EP98/03470

(22) International Filing Date: 30 May 1998 (30.05.98)

(30) Priority Data:
9713733.5 27 June 1997 (27.06.97) GB

(71) Applicant *(for all designated States except US)*: PHARMACIA & UPJOHN S.P.A. [IT/IT]; Via Robert Koch, 1.2, I–20152 Milan (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MONGELLI, Nicola [IT/IT]; Via Tertulliano, 38, I–20137 Milan (IT). CRUGNOLA, Angelo [IT/IT]; Via R. Settimo, 30, I–21100 Varese (IT). LOMBARDI BORGIA, Andrea [IT/IT]; Via Carso, 29, I–20067 Paullo (IT). CIOMEI, Marina [IT/IT]; Via Del Molo, 1, I–27020 Torre d'Isola (IT). ALBANESE, Clara [IT/IT]; Via G. Cadolini, 4, I–20137 Milan (IT). SOLA, Francesco [IT/IT]; Via G. Keplero, 10, I–20038 Seregno (IT).

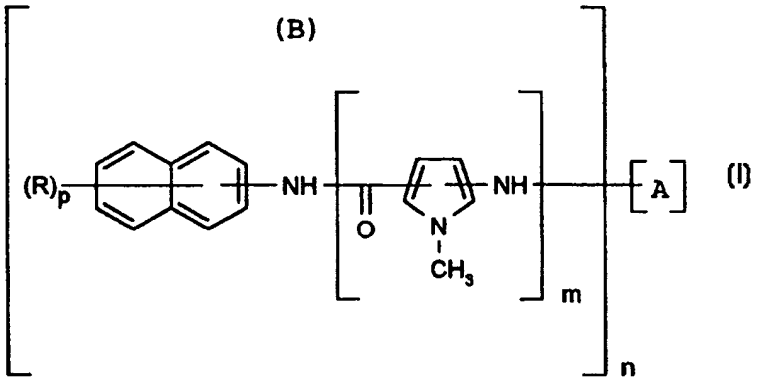
(81) Designated States: AL, AU, BG, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, TR, UA, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: POLY–BRANCHED POLYCARBOXAMIDO COMPOUNDS

(57) Abstract

New polycarboxamido compounds of formula (I), wherein n is an integer of 1 to 4; m is an integer of 1 to 6; p is an integer of 1 to 3; each of the R groups, which are the same in each single (B) group, is a free or esterified acidic group; [A] is a di–, tri– or tetra–carboxylic acid in which at least one carboxylic group is linked to a (B) group through an amidic bond and the remaining one(s) are free or esterfied carboxylic groups; and the pharmaceutically acceptable salts thereof, which are angiogenesis inhibitors, anti–lentivirus agents, and have TNFα–neutralizing activity are provided.



FOR THE PURPOSES OF INFORMATION ONLY

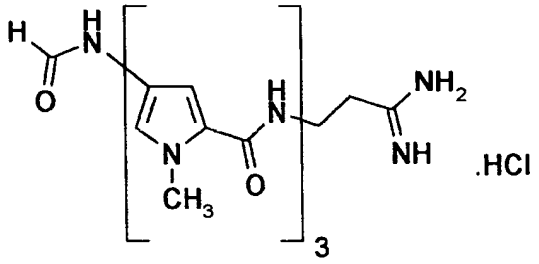
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

POLY-BRANCHED POLYCARBOXAMIDO COMPOUNDS

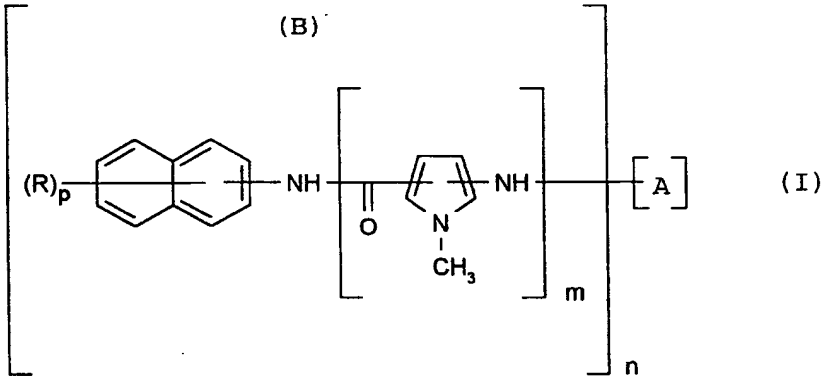
The present invention relates to new poly-branched polycarboxamido compounds, to a process for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The compounds of the invention may be regarded as derivatives of Distamycin A which is a known compound having the following formula



.HCl

The present invention provides polycarboxamido compounds having the following formula (I)



(I)

wherein

n an integer of 1 to 4;

m is an integer of 1 to 6;

p is an integer of 1 to 3;

each of the R groups, which are the same in each single (B) group, is a free or esterified acidic group;

[A] is a di-, tri- or tetra- carboxylic acid in which at

least one carboxylic group is linked to a (B) group through an amidic bond and the remaining one(s) are free or esterified carboxylic groups; and the pharmaceutically acceptable salts thereof.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bio-precursors of the compounds of the formula (I).

Examples of di,tri or tetra-carboxylic acids (A) are:

1,2,3-propanetricarboxylic acid (tricarballilic acid),

N,N-Bis(carboxymethyl)glycine (nitrilotriacetic acid),

2-(carboxymethyl)-1,3-propanedicarboxylic acid,

1,3,5-benzenetricarboxylic acid,

1,2,3-benzenetricarboxylic acid,

1,2,4-benzenetricarboxylic acid,

1,2,4,5-benzenetetracarboxylic acid (pyromellitic acid),

1,2,3,4-benzenetetracarboxylic acid,

1,2,3,5-benzenetetracarboxylic acid,

N,N'-1,2-ethanedylbis[N-(carboxymethyl)glycine] (EDTA).

Examples of carboxylic esters of acid (A) are for instance alkyl and aryl-alkyl esters, having a branched or straight alkyl chain. C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters, typically methyl, ethyl, propyl, iso-propyl, butyl, benzyl and phenylethyl esters are more preferred.

The free, salified or esterified R groups may be on either or both the phenyl moieties of the naphthalene group.

Examples of R acidic groups, according to the present invention, for instance are those chosen from the group including sulfonic, phosphonic and carboxylic acid groups, the sulfonic and phosphonic acid groups being the preferred.

Esters of said acidic groups are for instance alkyl and

aryl-alkyl esters, having a branched or straight alkyl chain. C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters, typically methyl, ethyl, propyl, iso-propyl, butyl, benzyl and phenylethyl esters are more preferred.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminum hydroxides, or with organic bases, such as lysine, arginine, N-methylglucamine, triethylamine, triethanolamine, dibenzylamine, methylbenzylamine, di-(2-ethylhexyl)amine, piperidine, N-ethylpiperidine, N,N-diethylaminoethylamine, N-ethylmorpholine, -phenethylamine, N-benzyl- -phenethylamine, N-benzyl-N,N-dimethylamine and the other acceptable organic amines. Sodium and potassium salts are preferred.

When n is 2, 3 or 4, the (B) groups may be the same or different. They may differ each other for the different acidic R groups and/or the different values of m and/or p, however they are preferably the same.

The substituted naphthyl groups are typically 1- or 2-aminonaphthyl groups.

When the naphthyl groups are substituted by three free, esterified or salified acid groups, as defined above, the acid substituents are preferably in the 4,6,8-, 3,6,8-, 3,7,8- positions.

When they are substituted by two free, esterified or salified acid groups, the acid substituents are preferably in the 1,5-, 3,6-, 3,8-, 4,6-, 4,7-, 4,8-, 5,7- or 6,8-positions.

When they are substituted by one free, esterified or salified acid group, the acid substituent is preferably in the 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8- position, of course is not linked to the amino position.

The amino and carbonyl groups may be independently linked to any of the 2 to 5 carbon positions of the pyrrole ring; of course, such groups are not both linked to the same carbon position. The disubstituted pyrroles are typically N-methyl-2,4-disubstituted pyrroles, preferably 1-methylpyrrole-4-amino-2-carbonyl and 1-methylpyrrole-2-amino-4-carbonyl derivatives.

As already said, the invention includes within its scope also the esters and the pharmaceutically acceptable salts of the acids of formula (I).

Only one or both of the two acidic functions of each phosphono $(HO)_2PO$-group are salified and/or esterified.

In the salts of the invention preferably only one of the two acidic functions of each phosphono group is in a salified form, whereas in the esters of the invention both the two acidic functions of each phosphono group are preferably in an esterified form.

As stated above, the present invention also includes within its scope pharmaceutically acceptable bio-precursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are converted directly or indirectly <u>in vivo</u> into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I) in which [A] is as defined above; m is 1 to 3; p is 2 or 3; n is 3 or 4; and each of the R groups, which are the same, is a free or esterified phosphonic or sulfonic acidic group; and the pharmaceutically acceptable salts thereof.

Examples of preferred compounds of the invention are:

1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane salt ;

1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,1',1"-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

1,3,5-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}benzene;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

1,2,3-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,1',1"-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

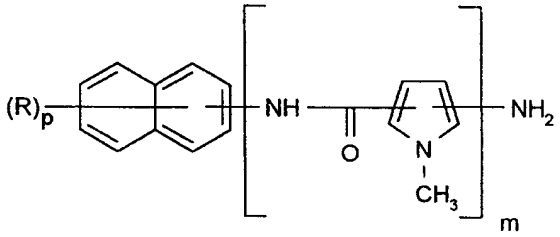
1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

and the C_1-C_6-alkyl and phenyl-C_1-C_6-alkyl esters and the pharmaceutically acceptable salts thereof.

Particularly preferred are the methyl, ethyl and benzyl esters and the sodium and potassium salts of the said examples of specific compounds of the invention.

The compounds of formula (I) and the pharmaceutically acceptable salts thereof are hereafter also referred to as "the compounds of the invention" or as "the active agents of the invention".

The compounds of the invention, and the salts thereof can be prepared by a process comprising reacting a compound of formula (II)

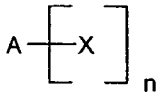


(II)

wherein

m, p and R are as defined above, or a salt thereof,

with a compound of formula (III)



(III)

wherein

each of the X groups, which may be the same or different, is a leaving group; and [A] and n are as defined above;

and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

A salt of a compound of formula (II) may be a salt with organic or inorganic bases, for example those mentioned above as to the pharmaceutically acceptable salts of the invention, the sodium and potassium salts being the preferred.

X may denote any suitable leaving group. It may denote a good leaving group, preferably a halogen atom, in particular chlorine, or another easily displaceable group such as imidazolyl, triazolyl, p-nitrophenoxy or trichlorophenoxy.

The reaction of a compound of formula (II), or a salt thereof, with a compound of formula (III) is an analogy process and can be carried out according to well known methods; for example according to the conditions described in organic chemistry for this kind of reaction, i.e. for synthesis of peptides. Preferably the reaction may be carried out at a molar ratio of compound (II), or a salt thereof : compound (III) from about 1 : 0.2 to about 1 : 4. The reaction is preferably performed in an organic solvent, such as dichloromethane, dichloroethane, chloroform, toluene, or dimethylsulphoxyde, dimethylformamide, dimethylacetamide, hexamethylphosphoramide, or their aqueous mixtures, or in water/dioxane, water/toluene or water/dichloromethane mixtures, in the presence of either an organic base such as triethylamine, diisopropylethylamine or pyridine or an inorganic base such as sodium bicarbonate or sodium acetate or a convenient buffer as known in the art. The reaction temperature may vary from about -10°C to about 150°C and the reaction time from about 1 to 24 hours.

The compounds of formula (I) prepared according to the above described procedures may be purified by conventional methods such as by silica gel, alumina or reversed phase column chromatography, and/or by recrystallization from organic solvents such as lower aliphatic alcohols or dimethylformamide or their mixtures or in water containing mixtures.

Analogously, esterification or salification of an acid of formula (I) can be carried out by known methods in the art. The compounds of formula (II) are known products and can be obtained according to PCT/EP91/00014 or to PCT/EP95/00444. The compounds of formula (III) are known compounds or may be obtained from known di-, tri-, or tetra-carboxylic acids according to well known methods in organic chemistry.

PHARMACOLOGY

The compounds of formula (I), and the pharmaceutically acceptable salts thereof, according to the present invention, are angiogenesis inhibitors, as shown, e.g., by the fact that they have been found to be active in the chorioallantoic membrane test, according to the Folkman's method [Nature, 297, 307 (1982)]. Therefore the compounds of the present invention are useful in treating several pathological conditions in mammals, including humans, where the growth of new blood vessels is detrimental, for example, in chronic inflammation, diabetic retinopathy, psoriasis, rheumatoid arthritis and tumor growth. In particular, in the cancer therapy the compounds of the invention can be administered alone or in association with antitumor agents such as doxorubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin or mitomycin.

The compounds of the present invention have also been found to be endowed with TNFα-neutralising activity and therefore they can be employed in humans for prophylactic and/or therapeutic use in any disease state in which TNFα is known to play a detrimental role. Typically such disease states are cachexia, septic shock, graft-versus-host disease,

AIDS, cerebral malaria, rheumatoid arthritis. The TNFα-inhibiting activity of the compounds according to the present invention is proven, for instance, by the fact that they are active in inhibiting the cytotoxicity activity of human TNF a on untreated mouse LM cells.

Accordingly, the new compounds of the invention can be used as angiogenesis inhibitors and/or as TNFα-neutralising activity agents. The compounds of the invention can thus be used in the preparation of a medicament for use in the treatment of angiogenesis and/or for prophylactic and/or therapeutic use in a disease state in which TNFα plays a detrimental role. In these therapeutical applications the compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally. The dosage depends on the age, weight and conditions of the patient and on the administration route. For example, a suitable dosage for administration to adult humans may range from about 0.5 to about 250 mg pro dose 1-4 times a day.

Moreover, the compounds of the present invention have been found to act directly as anti-lentivirus agents, in particular against Human Immunodeficiency Virus (HIV). For instance, the representative compounds of the invention 1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt, 1,1',1"-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt, have been found to be active in the biological test

described in J. Natl. Cancer Inst. 81, 557-586 (1989). A human patient suffering from lentivirus infection can thus be treated by a method comprising administering thereto an effective amount of one of the compounds of the invention. In this way, the compounds of the invention can be used to treat an infection attributable to a lentivirus, in particular a human immunodeficiency virus, especially HIV-1 or HIV-2.

The compounds of the invention can also be used in the preparation of a medicament for use in the treatment of a human patient suffering from lentivirus infection. The said medicament may be for use as an anti-lentivirus agent, for example an anti-HIV-1 or -HIV-2 agent. The said medicament may also be for use in ameliorating the symptoms of lentivirus-induced disease in a human patient suffering from lentivirus infection.

In particular the compounds of the invention can be used in the preparation of an agent to be used in the treatment of a human patient who is seropositive diseased, stressed or pathological as a result of infection with a lentivirus, in particular HIV, or who is suffering from induced disease, e.g., lymphoadenopathy syndrome (LS), AIDS-related complex (ARC), AIDS or Kaposi's sarcoma. The condition of a human patient can thus be ameliorated or improved.

In these therapeutical applications the compounds of the invention can be administered by usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection or infusion being preferred. The dosage depends on the age, weight and condition of the patient and on the administration route.

A suitable dosage for the compounds of the invention, for example 1,1',1"-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt or a pharmaceutically acceptable salt thereof, for administration to adult humans is from about 0.4 to about 250 mg per dose 1-4 times a day.

The compounds of the invention may be used in a method of treatment of the above mentioned pathological conditions comprising both separate and substantially contemporaneous administration of a composition containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing different pharmaceutically active agents. The present invention therefore further provides products comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a second active agent as a combined preparation for separate, simultaneous or sequential use in treating a human patient suffering from lentivirus infection, in particular infection with HIV. The second active agent is typically a drug that affects the pathogenesis of HIV-induced diseases.

For example, the compounds of the invention may be employed with various active agents, in particular those that affect reverse transcriptase, antimicrobial and antitumor agents or a mixture of two or more thereof. Drugs of interest include non-nucleoside reverse transcriptase inhibitors, e.g. nevirapine; nucleoside derivatives, e.g. zidovudine and didanosine; acyclovir; ribavirin; ascorbic acid; protease inhibitors; cytokine, e.g. IL-1, IL-2, IL-3 or IL-4; growth factors; interferons, e.g. alpha- or gamma-interferon; antitumor agents, e.g. doxorubicin,

daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, melphalan, cyclophosphamide, bleomycin, vinblastin and mitomycin; immunomodulating agents, in particular immunostimulants, gamma globulin, immune globulin and monoclonal antibody products, antibiotics and antimicrobial products.

Typically, the antimicrobial agents may include a penicillin in conjunction with an aminoglycoside (e.g. gentamycin, tobramycin).

However several well additional agents, e.g. cephalosporin, can be utilised.

The administration dosage of these drugs will vary, depending upon the disease status of the individual. The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

The pharmaceutical composition used in the invention may comprise a compound of formula (I) or pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers. The pharmaceutical compositions are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions. Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g.

propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine, methylcellulose, carboxymethylcellulose, polyvinylpyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The following examples illustrate but do not limit the invention.

Example 1

1,2,3-Tris(imidazole-1-carbonyl)propane [compound (III), n=3, X=imidazolyl, [A]=from tricarballilic acid].

Tricarballic acid (5.0 g, 28.38 mmol) was dissolved in dimethylformamide (20 ml) and 1-1'-carbonyldiimidazole (15.18 g, 93.6 mmol) was then added at room temperature.

The whole was stirred at RT until evolution of CO_2 ceased and then kept at +4°C overnight.

The precipitated microcrystalline solid was filtered, washed with DMF and diethyl ether and vacuum dried to give the title compound (1.68 g).

^{1}H NMR (DMSO-d_6): δ 8.6 (s, 1H); 8.4 (s, 2H); 7.8 (s, 1H); 7.7 (s, 2H); 7.1 (s, 1H); 7.0 (s, 2H); 4.2-4.4 (m, 1H); 3.5-3.8 (m, 4H).

Example 2

1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt [PNU 156752, compound (I), R=SO_3H, m=2, n=3, p=2, [A]=from tricarballilic acid].

A solution of 1,2,3-tris(imidazole-1-carbonyl)propane of example 1 (82 mg, 0.252 mmol) and 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid dipotassium salt hydrochloride (0.5 g, 0.757 mmol) in DMF (5 ml) was stirred at room temperature, under N_2 for 4 days.

The DMF was evaporated under reduced pressure, the residue dissolved in water and passed through a sulfonic acid ion-exchange resin in H^+ form. The acid eluate is neutralised to pH 7.0 with $NaHCO_3$ and purified by reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:CH_3CN 90:10. The product containing eluate is evaporated under reduced pressure and vacuum-dried to give the title compound as a yellow solid (134 mg).

(-)FAB MS (m/z): 1872 $(M-Na)^-$.

^{1}H NMR (DMSO-d_6): δ 2.42 (dd, 2H); 2.66 (dd, 2H); 3.33 (dd,

1H); 6.8-7.4 (m, 12H); 7.86 (m, 6H); 8.00 (m, 3H); 8.21 (m, 3H); 8.91 (m, 3H); 9.8-10.3 (m, 9H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt;

1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt;

1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane nonasodium salt;

1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt;

1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt;

1,2,3-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane hexasodium salt;

1,2,3-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane hexasodium salt;

1,2,3-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane nonasodium salt;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane hexasodium salt;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane hexasodium salt; and

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane nonasodium salt.

Example 3

With the imidazolyl derivatives of benzene-tri and tetra-carboxylic acids prepared as described in Example 1, by proceeding analogously to the procedure of Example 2, with the appropriate starting materials, the following compounds can be obtained:

1,3,5-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;

1,3,5-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;

1,3,5-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;

1,3,5-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene nonasodium salt;

1,3,5-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;

1,3,5-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene nonasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,4-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,4-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,4-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt;
1,2,4-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene nonasodium salt;
1,2,4-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt; 1,2,4-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene hexasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene dodecasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,3,4-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; 1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene dodecasodium salt;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene dodecasodium salt;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt; and

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene octasodium salt.

Example 4

With the imidazolyl derivative of 2-(carboxymethyl)-1,3-propanedicarboxylic acid prepared as described in Example 1, by proceeding analogously to the procedure of Example 2,

with the appropriate starting materials, the following compounds can be obtained:

tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane hexasodium salt;

tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane hexasodium salt;

tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane hexasodium salt;

tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane nonasodium salt;

tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane hexasodium salt; and

tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane hexasodium salt.

Example 5

1,1',1"-Tris(imidazole-1-carbonyl)trimethylamine [compound (III), X=imidazolyl, n=3, [A]=from nitrilotriacetic acid].

To a stirred suspension of nitrilotriacetic acid (2.5 g, 13.08 mmol) in dry-DMF (25 ml), 1,1'-carbonyldiimidazole

(7.42 g, 45.8 mmol) was added in small portions. The whole was stirred at RT until evolution of CO_2 ceased. After addition of Et_2O (50 ml), the precipitated solid was filtered, washed with Et_2O:DMF 2:1 and Et_2O and dried to give the title compound as a crystalline white solid (3.18 g).

^1H NMR (DMSO-d_6): δ 8.4 (m, 1H), 7.7 (m, 1H), 7.0 (m, 1H), 4.5 (s, 2H).

Example 6

1,1',1"-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt [PNU 159934, compound (I), R=SO_3H, m=2, n=3, p=2, [A]=from nitrilotriacetic acid].

A solution of 7-({4-[(4-amino-1-methylpyrrole-2-carbonyl)amino]-1-methylpyrrole-2-carbonyl}amino)naphthalene-1,3-disulfonic acid dipotassium salt hydrochloride (582 mg, 0.882 mmol) and 1,1',1"-tris(imidazole-1-carbonyl) trimethylamine of Example 5 (86 mg, 0.252 mmol) in dry DMF (10 ml) was stirred at RT for 4 days. The DMF was removed under reduced pressure, the residue treated with ethanol, stirred for 30 min and filtered. The solid thus obtained was dissolved in water and passed through a sulfonic acid ion-exchange resin in H^+ form. The acid eluate was neutralised to pH 7.0 with NaOH 1N and purified by reversed-phase liquid chromatography eluting with a gradient from H_2O to H_2O:CH_3CN 88:12 to give, after evaporation of the product containing fractions, 195 mg of the title compound as an orange solid.

^1H NMR (DMSO-d_6): δ 3.58 (s, 2H); 3.87 (s, 6H); 6.96, 7.21,

7.27, 7.31 (Four doublets, 4H); 7.86 (m, 2H); 8.00 (d, 1H); 8.21 (d, 1H); 8.91 (s, 1H); 9.94 (s, 1H); 10.18 (s, 2H).

By proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

1,1',1"-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt;

1,1',1"-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine nonasodium salt;

1,1',1"-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine hexasodium salt;

1,1',1"-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine hexasodium salt;

1,1',1"-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine hexasodium salt;

1,1',1"-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine nonasodium salt;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine hexasodium salt;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine hexasodium salt; and

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine nonasodium salt.

Example 7

With the imidazolyl derivative of EDTA prepared as described in Example 5, by proceeding analogously, with the appropriate starting materials, the following compounds can be obtained:

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine octasodium salt;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine octasodium salt;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine octasodium salt;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine dodecasodium salt;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine octasodium salt; and

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine octasodium salt.

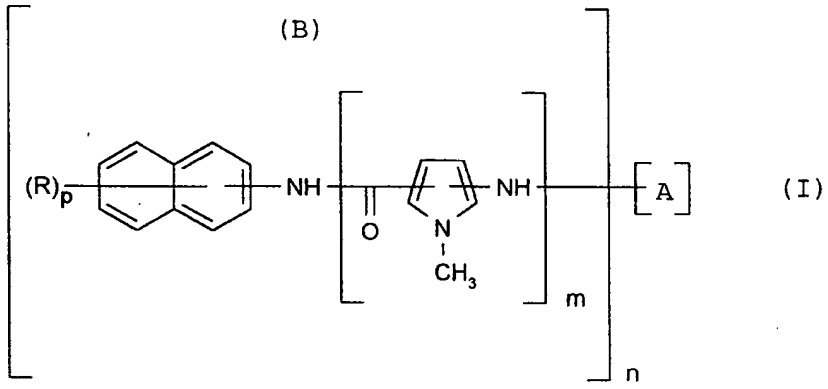
Example 8

Intramuscular injection 30 mg/ml.

An injectable pharmaceutical preparation can be manufactured by dissolving 30 g of 1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane hexasodium salt in water for injection (1000 ml) and sealing ampoules of 1-10 ml.

CLAIMS

1. A polycarboxamido compound of formula (I)



(I)

wherein

n an integer of 1 to 4;

m is an integer of 1 to 6;

p is an integer of 1 to 3;

each of the R groups, which are the same in each single (B) group, is a free or esterified acidic group;

[A] is a di-, tri- or tetra- carboxylic acid in which at least one carboxylic group is linked to a (B) group through an amidic bond and the remaining one(s) are free or esterified carboxylic groups; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to claim 1, wherein each R acid group is independently chosen from sulfonic, phosphonic and carboxylic acid groups.

3. An ester of a compound of formula (I), as defined in claim 1, wherein said ester is a C_1-C_6 alkyl or a phenyl-C_1-C_6 alkyl ester.

4. A compound of formula (I), as defined in claim 1,

in which m is 1 to 3; p is 2 or 3; n is 3 or 4; and each of the R groups, which are the same, is a free or esterified phosphonic or sulfonic acidic group; or a pharmaceutically acceptable salt thereof.

5. A compound selected from:

1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane salt ;

1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}propane;

1,1',1"-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

1,1',1"-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}trimethylamine;

tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}methane;

1,3,5-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,3,5-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4-tris{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-

methylpyrrole-4-amino]carbonyl}benzene;

1,2,4,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,4-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-

7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

1,2,3,5-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}benzene;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-disulfonic acid-2-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,7-diphosphonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

N,N,N',N'-tetra{[2-({2-[(naphthalene-1,5-diphosphonic acid-3-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonylmethyl}ethane-1,2-diamine;

1,2,3-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-

amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,2,3-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]propane;

1,1',1"-tris({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)trimethylamine;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3-disulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,7-disulfonic acid-4-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

1,1',1"-tris[(2-{[2-({2-[(naphthalene-1,3,5-trisulfonic acid-7-amino)carbonyl]-1-methylpyrrole-4-amino}carbonyl)-

1-methylpyrrole-4-amino]carbonyl}-1-methylpyrrole-4-amino)carbonyl]trimethylamine;

or a C_1-C_6-alkyl or phenyl-C_1-C_6-alkyl ester, or a pharmaceutically acceptable salt thereof.

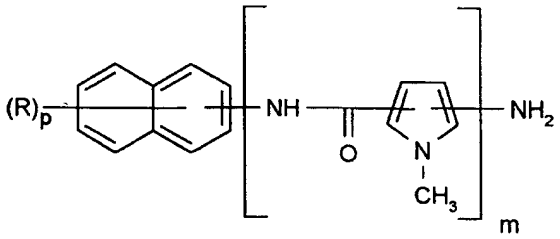
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and, as an active compound, a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as angiogenesis inhibitor.

8. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as TNFα-neutralizing activity agent.

9. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, for use as anti-lentivirus agent.

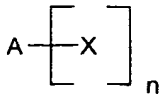
10. Process for the preparation of a compound of formula (I), as defined in claim 1, or a salt thereof, said process comprising reacting a compound of formula (II)



(II)

wherein

m, p and R are as defined in claim 1, or a salt thereof, with a compound of formula (III)



(III)

wherein

each of the X groups, which may be the same or different, is a leaving group; and [A] and n are as defined in claim 1, and, if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired, salifying a compound of formula (I) thus obtained, and/or, if desired obtaining a free acid of formula (I) from an ester or a salt thereof, and/or, if desired, esterifying an acid of formula (I).

INTERNATIONAL SEARCH REPORT

Interr. ial Application No
PCT/EP 98/03470

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26950 A (PHARMACIA) 6 September 1996 see claims 1,8,9	1,5-7
A	WO 94 23718 A (PHARMACIA/FARMITALIA) 27 October 1994 see claims 1,6	1,5,6,9
A	WO 95 23806 A (PHARMACIA) 8 September 1995 see claims 1,6-10	1,5-9
A	WO 91 10649 A (FARMITALIA CARLO ERBA) 25 July 1991 see claims 1,7-10	1,5-8
A	GB 2 261 661 A (FARMITALIA CARLO ERBA) 26 May 1993 see claims 1,7-9	1,5-7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1998	12/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/EP 98/03470

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	GB 2 310 207 A (PHARMACIA & UPJOHN) 20 August 1997 see claims 1,6-10	1,5-9

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 98/03470

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626950 A	06-09-1996	AU 696470 B	10-09-1998
		AU 4869896 A	18-09-1996
		CA 2189358 A	06-09-1996
		CN 1148391 A	23-04-1997
		EA 6 B	30-12-1997
		EP 0758339 A	19-02-1997
		FI 964331 A	01-11-1996
		HU 9603305 A	28-08-1997
		JP 10504319 T	28-04-1998
		NO 964610 A	31-10-1996
		PL 317094 A	17-03-1997
WO 9423718 A	27-10-1994	AU 670194 B	04-07-1996
		AU 6537194 A	08-11-1994
		CA 2137148 A	27-10-1994
		CZ 9500107 A	13-09-1995
		EP 0646004 A	05-04-1995
		HU 71838 A	28-02-1996
		JP 7508044 T	07-09-1995
		NO 944809 A	12-12-1994
		PL 306798 A	18-04-1995
WO 9523806 A	08-09-1995	AU 678704 B	05-06-1997
		AU 1848895 A	18-09-1995
		CA 2160250 A	08-09-1995
		CN 1124027 A	05-06-1996
		EP 0696287 A	14-02-1996
		FI 955180 A	30-10-1995
		HU 74987 A	28-03-1997
		JP 8509992 T	22-10-1996
		NO 954346 A	30-10-1995
		NZ 281205 A	29-01-1997
		PL 311339 A	05-02-1996
		US 5700788 A	23-12-1997
		ZA 9501653 A	08-12-1995
WO 9110649 A	25-07-1991	AT 131810 T	15-01-1996
		AU 647446 B	24-03-1994
		AU 7059991 A	05-08-1991
		BG 60534 B	28-07-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter .ial Application No
PCT/EP 98/03470

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9110649 A		CA 2050331 A	12-07-1991
		CN 1053230 A,B	24-07-1991
		CS 9100056 A	15-10-1991
		DE 69115570 D	01-02-1996
		DK 462258 T	29-01-1996
		EP 0462258 A	27-12-1991
		ES 2084153 T	01-05-1996
		FI 99011 B	13-06-1997
		GR 3018767 T	30-04-1996
		HU 211237 B	28-11-1995
		IE 69462 B	18-09-1996
		IL 96875 A	30-03-1995
		JP 4504426 T	06-08-1992
		MX 9203119 A	01-07-1992
		NO 176274 B	28-11-1994
		PT 96455 A,B	15-10-1991
		SI 9110025 A	31-10-1996
		RU 2078079 C	27-04-1997
		US 5420296 A	30-05-1995
		US 5593976 A	14-01-1997
		US 5260329 A	09-11-1993
GB 2261661 A	26-05-1993	NONE	
GB 2310207 A	20-08-1997	NONE	